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Related Articles, Links

A pyrazole derivative, YM-58483, potently inhibits store-operated sustained Ca2+ influx and IL-2 production in T lymphocytes.

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In nonexcitable cells, Ca(2+) entry is mediated predominantly through the store depletion-dependent Ca(2+) channels called store-operated Ca(2+) (SOC) or Ca(2+) release-activated Ca(2+) channels. YM-58483, a pyrazole derivative, inhibited an anti-CD3 mAb-induced sustained Ca(2+) influx in acute T cell leukemia, Jurkat cells. But it did not affect an anti-CD3 mAb-induced transient intracellular Ca(2+) increase in Ca(2+)-free medium, nor anti-CD3 mAb-induced phosphorylation of phospholipase Cgamma1. It was suggested that YM-58483 inhibited Ca(2+) influx through SOC channels without affecting the TCR signal transduction cascade. Furthermore, YM-58483 inhibited thapsigargin-induced sustained Ca (2+) influx with an IC(50) value of 100 nM without affecting membrane potential. YM-58483 inhibited by 30-fold the Ca(2+) influx through SOC channels compared with voltage-operated Ca(2+) channels, while econazole inhibited both SOC channels and voltage-operated Ca(2+) channels with an equivalent range of IC(50) values. YM-58483 potently inhibited IL-2 production and NF-AT-driven promoter activity, but not AP-1-driven promoter activity in Jurkat cells. Moreover, this compound inhibited delayed-type hypersensitivity in mice with an ED(50) of 1.1 mg/kg. Therefore, we concluded that YM-58483 was a novel store-operated Ca(2+) entry blocker and a potent immunomodulator, and could be useful for the treatment of autoimmune diseases and chronic inflammation. Furthermore, YM-58483 would be a candidate for the study of capacitative Ca(2+) entry mechanisms through SOC/CRAC channels and for identification of putative Ca(2+) channel genes.

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